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Gene Section
Review

MIR122 (microRNA 122)

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Abstract

Review on MIR122, with data on DNA/RNA and where the gene is implicated.

Identity

Other names: MIR122A, MIRN122, MIRN122A, hsa-mir-122, miRNA122, miRNA122A

HGNC (Hugo): MIR122

Location: 18q21.31

Local order: miRNA-122 is located on the positive strand of chromosome 18 at 18q21.31. It is between base pairs 56118306-56118390 and is composed of 85 nucleotides encoding a single exon. NCBI gene ID is 406906.

The genes located on the chromosome near miRNA-122, listed in order from centromere to telomere on Mapviewer Master Map.

Genes on sequence are:

- LOC100132992 NMGN1P30 (18q21.31, negative strand): high mobility group nucleosome binding domain 1 pseudogene 30;
- NEDD4L (18q21, positive strand): neuronal precursor cell expressed developmentally down-regulated 4-like, E3 ubiquitin protein ligase;
- **MIR122 (18q21.31, positive strand): microRNA-122**;
- MIR3591 (negative strand): microRNA-3591;
- ALPK2 (18q21.31, negative strand): alpha-kinase 2;
- RPL9P31 (18q21, positive strand): ribosomal protein L9 pseudogene 31.

Note

miR-122 clusters with miR-3591, which is located on the negative strand of chromosome 18 between base pairs 56118312-56118384. miR-3591 is part of the miR-122 gene family and is processed into two different mature forms (miRBase).

DNA/RNA

Note

miR-122 sequence:

Pre-miRNA sequence:

5'-CCUUAGCAGAGCUGUGGAGUGUGACAAUGGUGUUUGUGUCUAAACUAUCAAACGCCAUUAUCACACUAAAUAGCUACUGCUAGGC-3'

Mature miR-122 sequences associated with this pre-miRNA sequence:

MIR 122-5P 15-UGGAGUGUGACAAUGGUGUUUG-36

MIR 122-3P 51-AACGCCAUUAUCACACUAAAUA-72

Primary isoforms of miR-122-5P:

UGGAGUGAGACAAUGGUGUUU

UGGAGUGAGACAAUGGUGUUUG

(Sequences from miRBase.)

Figure1. Genomic context for chromosome 18 surrounding MIR122 (figure adapted from NCBI Gene).

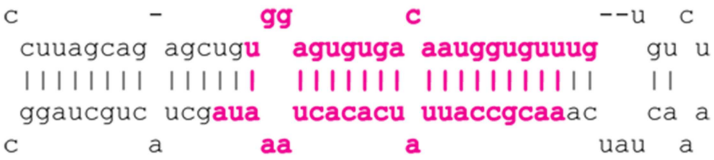

Figure 2. Stem-loop structure of pre-miR-122. The pink highlighted regions indicate the mature miR-122 duplex; the top pink sequence is the hsa-miR-122-5P sequence and the bottom pink sequence is the hsa-miR-122-3P sequence (diagram adapted from miRBase).

Description

The coding sequence for microRNA-122 (miR-122) comprises a single locus on the human chromosome 18 (Jopling, 2012). After transcription and processing, miR-122 is loaded onto an RNA-Induced Silencing Complex (RISC), comprised of Argonaute 2 (Ago-2), GW182, and other proteins (Wilson and Huys, 2013), where the miRNA duplex is unwound and one strand, the "guide strand" is retained and the other strand, the "passenger strand", is discarded. The miRNA guide strand directs the RISC to target mRNAs based on imperfect sequence complementarity. Important base-pairing occurs between nucleotides 2 - 8 of the miRNA (the seed sequence) and the 3' un-translated region (UTR) of the target mRNA (Du and Zamore, 2005). RISC binding directs the repressed mRNA to a processing (P)-body, where the mRNA is sequestered and/or degraded (Wilson and Huys, 2013). miR-122 antagonism shows that miR-122 regulates, directly or indirectly, at least 199 liver mRNAs (Elmén et al., 2008).

Transcription

miRNA messenger RNAs are transcribed by RNA polymerase II, which generates a primary miRNA transcript (pri-miRNA) (Saj and Lai, 2011). Pri-miRNAs can encode a single miRNA, or multiple miRNAs expressed as a cluster (Arora et al., 2013). Unspliced pri-miR-122 is 7506 bp in length and only encodes miR-122; following splicing, the pri-miR-122 transcript is 4543 bp (Li et al., 2011). The spliced pri-miRNA contains a miR-122 stem-loop that is cleaved by a complex of Drosha, a nuclear RNase III enzyme, and DGCR8, a double-stranded RNA-binding protein to form the pre-miR-122 hairpin (Saj and Lai, 2011; Arora et al., 2013). The pre-miRNA is exported from the nucleus and cleaved once more in the cytoplasm by Dicer, an RNase III enzyme, resulting in the double-stranded miRNA duplex (figure 2) (Saj and Lai, 2011).

Studies have shown that expression of human miR-122 is highest in liver tissues, but is also detected in the nervous and respiratory systems (Landgraf et al., 2007).

The same study showed that miR-122 is differentially expressed in cells of hematopoietic lineage (Landgraf et al., 2007).

Regulation of miR-122 expression is not fully characterized, but involves liver enriched transcription factors (LETFs). LETF HNF4α binds to the miR-122 promoter region and positively regulates miR-122 expression in human hepatoma Huh-7 cells and in mouse liver (Li et al., 2011).

Increased miR-122 results in activation of a number of transcriptional targets associated with , one of the key central regulators involved in miR-122 gene activation (Coulouarn et al., 2009).

Other liver factors proposed to control miR-122 expression include HNF1A, HNF3A and HNF3B: a decrease in any of these factors results in reduced miR-122 expression; the same trend also occurs with HNF4G and HNF6 but to a lesser extent (Coulouarn et al., 2009). HNF6 is also part of a positive feedback loop that includes miR-122 and stimulates expression of various hepatocyte-specific genes and other LETFs required for hepatocyte differentiation (Laudadio et al., 2012).

In addition, peroxisome proliferator activated receptor-gamma (PPARγ) and retinoid X receptor alpha (RXRα), can transcriptionally activate miR-122 (Song et al., 2013), but interestingly PPARγ inhibits miR-122 expression when bound by the hepatitis B virus X protein (Song et al., 2013).

The variety of transcription factors that have direct or indirect roles on miR-122 expression allude to its multitude of functions.

Protein

Note

There is no protein associated with MIR 122.

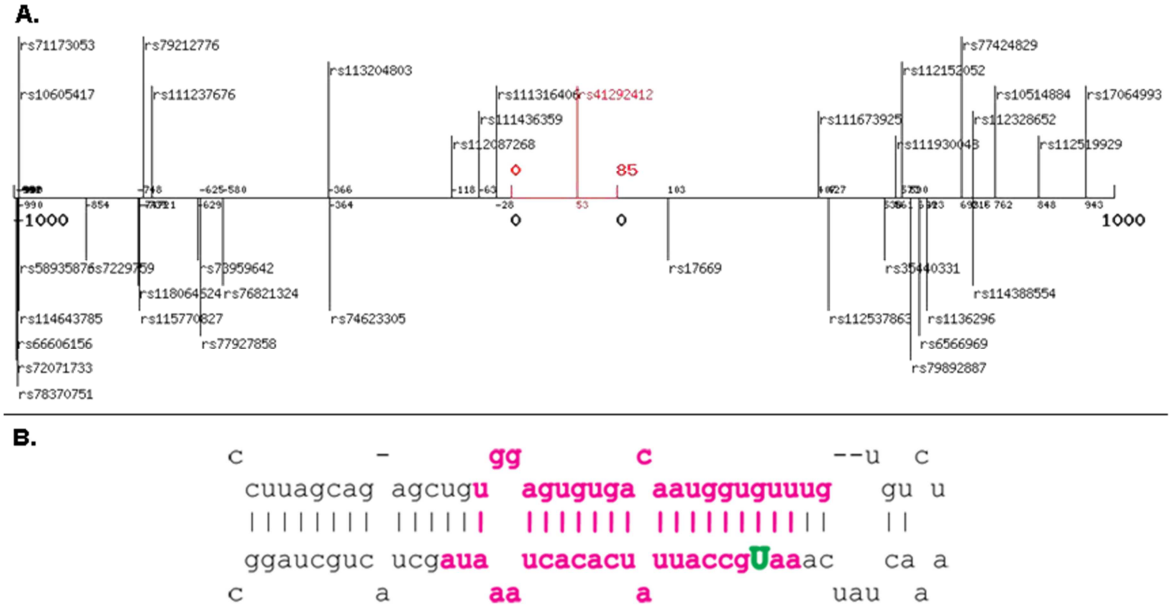

Figure 3. A. Location of SNPs near the mature miR-122 coding sequence. The highlighted region is the miR-122 sequence and the location of rs41292412 is indicated by the red line (diagram adapted from miRNASNP). **B.** Location of rs4129412 (green: C to T mutation in the chromosomal coding) in the miR-122 duplex (modified from miRBase).

Mutations

Note

There are 72 single nucleotide polymorphisms (SNPs) associated with the miR-122 transcript, but only one is found within the mature miR-122 sequence. The SNP ID is rs41292412, a C to T mutation located in the chromosome at 56118358, within the hsa-miR-122-3P mature sequence. Other SNPs can be found on NCBI database; GeneCards; and microRNA-related single nucleotide polymorphisms (miRNASNP).

Germinal

No.

Somatic

Yes.

Implicated in

Hepatocellular carcinoma (HCC)

Note

miR-122 has been identified as a tumour-suppressor microRNA; loss of miR-122 expression has been observed in cases of hepatocellular carcinoma, and its function in suppressing tumour-like functions have been verified in animal and cell culture models (Bai et al., 2009; Coulouarn et al., 2009; Hsu et al., 2012; Kutay et al., 2006).

Prognosis

In miR-122 knockout mice, addition of exogenous miR-122 strongly suppressed tumourigenesis (Hsu et al., 2012). Restoration of miR-122 expression to hepatocellular carcinoma cells increased their sensitivity to chemotherapeutics adriamycin and vincristine; this was also marked by miR-122-mediated reduction of MDR-1, GST-π, MRP, Bcl-w, and Cyclin B1, aiding in induction of cell cycle arrest (Xu et al., 2011). Addition of miR-122 to HCC cells also rendered them more susceptible to doxorubicin treatment (Fornari et al., 2009). miR-122 is believed to aid many chemotherapeutic agents in hepatocellular carcinoma by downregulating the unfolded protein response, permitting therapeutic apoptosis that would otherwise be suppressed in cancer cells (Yang et al., 2011). The level of miR-122 in human serum is also being explored as a potential biomarker to detect hepatocellular carcinoma development and progression (Ding et al., 2012).

Oncogenesis

miR-122 is hypothesized to regulate terminal hepatocyte differentiation, and loss of its expression (with subsequent upregulation of stem cell-associated proteins such as Pkm2) is a potential step towards hepatocellular carcinoma development (Jung et al., 2011). Loss of expression in HCC tumour samples and cell lines resulted in acquisition of migration and invasive properties (Coulouarn et al., 2009; Tsai et al., 2009). Exogenous miR-122 was found to limit cell growth and promote apoptosis in hepatocellular carcinoma cell lines by suppressing Wnt1, which disrupts the canonical Wnt/β-catenin proliferation pathway (Xu et al., 2012). A subset of individuals with HCC have also been identified to bear a polymorphism (rs3783553) in the 3' UTR of IL-1α which is

hypothesized to disrupt a miR-122 binding site. IL-1α is implicated in carcinogenesis and tumour growth, as well as immune responses to tumours, and miR-122 regulation of IL-1α under normal circumstances may be an aspect of its tumour suppressor function (Gao et al., 2009). miR-122 knockout mice are observed to develop hepatosteatosis, hepatitis, and hepatic tumours (Hsu et al., 2012). Increases in oncogenic pathways, along with inflammation and pro-inflammatory cytokine production such as IL-6 and TNF were also observed in the livers of these mice (Hsu et al., 2012).

Cutaneous T-cell lymphoma (CTCL)

Oncogenesis

miR-122 is not normally expressed to high levels in T-cells, but has been identified in CTCL to be induced by p53 in response to chemotherapy, and reduce apoptosis of lymphomatous cells by stimulating Akt kinase with an unknown mechanism (Manfè et al., 2012). This is contrary to its normal pro-apoptotic (tumour suppressor) function in other cancers such as hepatocellular carcinoma.

Gastrointestinal cancers

Note

Although miR-122 is not expressed in high levels within the intestinal tract, it was found to be downregulated in both primary tumours and gastrointestinal cancer cell lines, in comparison to normal tissues (Wang et al., 2009). In a rat model of colorectal cancer, this downregulation in healthy tissues was predictive of carcinogenesis elsewhere in the colon, and could be monitored from fecal colonocytes in the stool (Kunte et al., 2012).

Oncogenesis

It is implicated in partnering with the tumour suppressor gene APC (adenomatous polyposis coli), which degrades β-catenin and prevents proliferative signaling, as sequestration of miR-122 reversed APC-mediated growth inhibition, while addition of exogenous miR-122 restored growth inhibition in uncontrolled cells (Wang et al., 2009).

Pancreatic adenocarcinoma

Note

miR-122 was found to be underexpressed in ductal pancreatic adenocarcinoma samples (Papaconstantinou et al., 2013).

Breast cancer

Note

miR-122 was identified in serum deep sequencing of stage II-III breast cancer patients, with increased levels of miR-122 correlating with and later predicting non-responsiveness to neoadjuvant chemotherapy and metastatic outcomes (Wu et al., 2012).

Tumour suppressor activity

Note

miR-122 has been implicated as a tumour suppressor in several different conditions, particularly hepatocellular carcinoma (Bai et al., 2009; Coulouarn et al., 2009; Hsu et al., 2012; Kutay et al., 2006). In hepatocellular carcinoma cell lines, it is believed to inhibit proliferation by suppressing Wnt/β-catenin signaling (Xu et al., 2012). miR-122 was determined to stabilize the tumour suppressor protein p53 by modulating Cyclin G1, with the added effect of enhancing hepatocellular carcinoma cells' susceptibility to treatment with doxorubicin (Fornari et al., 2009). Its expression is also inversely correlated with levels of the protein Pkm2, found in hepatocellular carcinomas (Jung et al., 2011). A subset of individuals with HCC bear a polymorphism (rs3783553) in the 3' UTR of IL-1α which is hypothesized to disrupt a miR-122 binding site. IL-1α is implicated in carcinogenesis and tumour growth, as well as immune responses to tumours, and miR-122 regulation of IL-1α under normal circumstances may be an aspect of its tumour suppressor function (Gao et al., 2009). Loss of miR-122 expression led to increased cell migration and invasion, while restoration of miR-122 suppressed these effects (Coulouarn et al., 2009). miR-122 gene knockout mice are prone to hepatic tumour development, while delivery of miR-122 to these mice strongly inhibited tumourigenesis (Hsu et al., 2012).

In anaplastic thyroid cancer, miR-122 levels increase in thyroid cancer cell lines that respond to treatment with a PAX8/PPARγ fusion protein, both in vitro and in xenografts (Reddi et al., 2013).

Lipid metabolism

Note

Microarrays have shown that miR-122 antagonism decreases the expression of several genes crucial to lipid metabolism, including ACC1, ACC2, ACLY, SCD1, and SREBP2, which contribute to fatty acid metabolism, and PMVK, which is essential for cholesterol biosynthesis (Esau et al., 2006). These mRNAs are not predicted to be direct targets of miR-122, so it is hypothesized that miR-122 may indirectly promote their expression by suppressing a transcriptional repressor (Esau et al., 2006). Consistent with these findings, miR-122 antagonism decreases serum cholesterol levels in chimpanzees (Lanford et al., 2010). Recently, Hsu et al. (2012) used miR-122 knock-out mice to identify AGPAT1 and CIDEC as direct targets of miR-122. CIDEC, also called FSP27, is associated

with lipid droplets and regulates triglyceride storage and fatty acid oxidation at these sites (Keller et al., 2008; Vilà-Brau et al., 2013). In the liver, CIDEC is induced during the initial stages of fasting, but decreases during late fasting (Vilà-Brau et al., 2013). CIDEC is believed to be regulated by the PKA-CREB-CRTC2 pathway (Vilà-Brau et al., 2013), and the role of miR-122 in CIDEC regulation remains to be determined.
AGPAT1 is involved in regulating the energy state in adipose and muscle tissues (Takeuchi and Reue, 2009). Overexpression studies show that AGPAT1 stimulates the conversion of fatty acids into triglycerides (Ruan and Pownall, 2001). Translational repression, mediated by miR-122 and the RISC, reduces the expression of CIDEC and AGPAT1 in hepatocytes (Hsu et al., 2012), and this inhibits the storage of triglycerides in liver tissue. miR-122 also directly targets cationic amino acid transporter 1 (CAT-1) mRNA (Chang et al., 2004), a membrane transporter expressed predominantly in peripheral tissues.
In summary, research has demonstrated that miR-122 directly and indirectly regulates lipid metabolism in the liver, but the mechanism of indirect regulation is unknown.

Liver damage

Note

Serum miR-122 has been identified as a potential biomarker for liver damage from many sources (Laterza et al., 2013). While some studies determine that serum miR-122 can be used to differentiate between different types of liver damage, especially when combined with other serum miRNAs, a comprehensive study has not yet been done to generate a diagnostic signature for the different causes of liver damage investigated. In both human and murine models of liver damage from alcohol and from Hepatitis B, miR-122 levels were elevated under damaged conditions, with levels correlating to disease scoring and severity (Zhang et al., 2010). In response to acute hepatotoxicity in humans, Ding et al. found miR-122 levels correlated with serum ALT levels, and further noted that when comparing HBV-associated liver damage to HCC-associated liver damage, the miR-122 profiles were distinct (Ding et al., 2012). miR-122 levels correlated with disease severity - although not viral titer - in chronically HCV-infected patients, and in patients with non-alcoholic fatty liver disease (Cermelli et al., 2011). In a rat model of liver transplantation, plasma miR-122 was evaluated as a marker of pending transplant rejection. In this instance, miR-122 expression was up-regulated upon liver damage (pre-transplantation), but did not signal transplant rejection (Hu et al., 2013). However, in human liver transplants, not only was miR-122 identified as a biomarker for liver damage, its expression was also significantly increased prior to and during acute transplant rejection (Farid et al., 2012). Starkey Lewis et al. demonstrated increased serum levels of miR-122 in patients experiencing acute acetaminophen poisoning, and observed that miR-122 levels were higher than with other forms of acute liver damage (Starkey Lewis et al., 2011). Finally, in a mouse model system, Bala et al. noted that the circulating form of miR-122, in combination with elevated or reduced levels, could be used to not only detect liver damage, but also to differentiate between causes: drug-induced injury led to miR-122 being found in the protein fraction of the mouse serum, while alcohol and inflammation-induced liver damage led to circulation of miR-122 in exosomes (Bala et al., 2012).

Liver development

Note

Hepatocyte nuclear factor 6 (HNF6), a hepatocyte-specific transcription factor, promotes miR-122 expression in hepatocytes (Laudadio et al., 2012). miR-122, in turn, enhances the expression of HNF6 and other liver-enriched transcription factors (LETFs), establishing a positive-feedback loop (Laudadio et al., 2012).
Along with other LETFs, HNF6 participates in a network of transcriptional regulation essential for the terminal differentiation of hepatocytes (Kyrmizi et al., 2006).
miR-122 also downregulates CUTL1, a transcription factor that represses genes required for hepatocyte differentiation (Xu et al., 2010), thus promoting hepatocyte differentiation.

Circadian rhythm

Note

Circadian expression of the miR-122 locus is under the control of two retinoid-related orphan receptor elements (ROREs) (Gatfield et al., 2009), on which REV-ERBα acts (Ueda et al., 2002).
REV-ERBα is a transcription factor that plays key roles in the regulation of circadian transcriptional feedback loops (Reppert and Weaver, 2002). In the mouse liver, mature miR-122 levels remain relatively constant, but pre- and pri-miR-122 levels fluctuate over the course of the circadian cycle (Gatfield et al., 2009).
The levels of these intermediates are lowest at Zeitgeber Time (ZT) 8-12 and highest at ZT24, and these periods correspond to the peak and minimal expression of REV-ERBα (Gatfield et al., 2009). Many miR-122 targets also demonstrate circadian fluctuations in expression that are concomitant with miR-122 fluctuation (Gatfield et al., 2009).

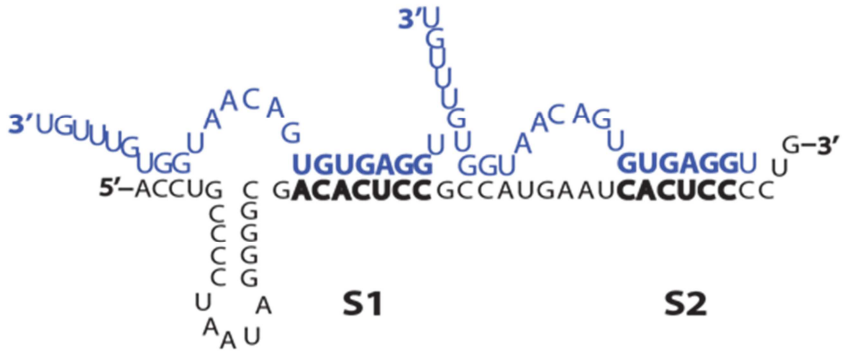

Figure 4. Two molecules of miR-122 (blue) binding to the 5' UTR of the HCV RNA (black) with the seed sequence in bold. Binding outside of the seed sequence is shown by un-bolded pairing of miR-122 and viral RNA (Thibault et al., 2013).

Iron homeostasis

Note

miR-122 directly targets the hemochromatosis (Hfe) and hemojuvelin (Hjv) mRNAs for suppression (Castoldi et al., 2011). Hfe and Hjv activate hepcidin, a hormone that controls systemic iron levels (Nemeth et al., 2004). Hepcidin binds to and induces the degradation of ferroportin, an iron efflux channel expressed on cells able to release iron, including macrophages and hepatocytes (Castoldi and Muckenthaler, 2012). By suppressing the activators of hepcidin, miR-122 prevents hepcidin from interacting with ferroportin (Castoldi et al., 2011). This model is supported by the observation that miR-122 depletion leads to iron deficiency (Castoldi et al., 2011).

Hepatitis C virus (HCV) infection

Note

HCV RNA bears two miR-122 binding sites in its 5' UTR (Jopling et al., 2008; Jopling et al., 2005). miR-122 binding has been shown to be critical to the viral life cycle by enhancing viral stability and translation, as well as other possible mechanisms that have yet to be determined, and has been proposed as the factor that defines the virus' liver tropism (Henke et al., 2008; Sedano, 2012; Shimakami et al., 2012). This interaction requires the miRNA RISC protein Argonaute-2, but is otherwise non-canonical, as the miRNA binds both with its seed sequence and with other sequences to the 3' end of the miRNA (Machlin et al., 2011; Wilson et al., 2011). Along with the role it plays in the virus life cycle, miR-122 has been identified as a potential serum marker for HCV-induced liver damage and hepatocellular carcinoma (Bihrer et al., 2011; Cermelli et al., 2011; Ding et al., 2012; van der Meer et al., 2013).

Disease

Hepatitis C Virus is a blood-borne infection that frequently progresses to chronicity, and can lead to liver-associated diseases such as metabolic syndrome, steatosis, cirrhosis, decompensated liver disease and liver failure, and hepatocellular carcinoma. It can also have extra-hepatic manifestations such as cryoglobulinemia and other auto-immune disorders, or neurological symptoms such as depression and cognitive impairment (Maasoumy and Wedemeyer, 2012).

Prognosis

HCV infection can be cured in a growing number of patients, as new direct-acting antiviral therapies are developed. Current treatment involves a lengthy course of pegylated interferon-alpha injections and ribavirin; for patients infected with HCV genotype 1, the protease inhibitors Telaprevir or Boceprevir are included in the treatment. Host genetics and health status, along with viral genotype, strongly influence the potential effectiveness of treatment. Without treatment, infection can progress to the diseases above (Myers et al., 2012; Ramachandran et al., 2012).

Oncogenesis

A proportion of patients with a chronic hepatitis C virus infection progress to hepatocellular carcinoma, although the mechanisms of oncogenesis are not yet firmly identified. The virus' proteins have been implicated in manipulating host cell signaling by downregulating, upregulating, or sequestering host factors (including the tumour-suppressor miR-122), leading to oncogenesis. Finally, as HCV is a chronic infection, the immunopathology from long-term low-grade inflammation can cause fibrosis, promoting cirrhosis and eventually carcinogenesis (Bühler and Bartenschlager, 2012).

Hepatitis B virus (HBV) infection

Note

Loss of miR-122 in hepatitis B virus infection leads to increased viral replication; miR-122 was shown to suppress Cyclin G1 expression, which in turn releases the antiviral and anti-tumour protein p53 (Wang et al., 2012b). Conversely, addition of miR-122 was shown to inhibit HBV replication, and was proposed to limit HBV-associated hepatocellular

carcinoma by suppressing NDRG3 (Fan et al., 2011). miR-122 has also been shown to directly bind to conserved HBV sequences, suppressing viral replication; in apparent response to this, the HBx viral protein inhibits miR-122 expression by binding PPARγ, a transcriptional activator of miR-122 (Chen et al., 2011; Song et al., 2013).
In addition, HBV has been observed to overproduce the targeted transcript to act as a miR-122 sponge (Li et al., 2013). miR-122 has been proposed as a serum marker for HBV-associated liver damage and hepatocellular carcinoma, as a means of detecting active and occult HBV infections, and of predicting patient risk of HBV disease progression (Chen et al., 2012; Ding et al., 2012; Qi et al., 2011; Waidmann et al., 2012; Zhang et al., 2010).

Disease

Hepatitis B virus infection is a blood-borne infection that progresses to chronicity in about 5% of adult acute infections, although the risk is much higher in children and infants (Kuo and Gish, 2012). The most common and most severe complications from HBV infection are liver cirrhosis, hepatic decompensation, and hepatocellular carcinoma, although extrahepatic manifestations associated with immune complex-mediated injury are also fairly frequent (Liang, 2009; Nebbia et al., 2012).
HBV-infected patients are also at risk from co-infection with a dependovirus, hepatitis D virus, which can only replicate in the presence of HBV, as it uses HBV proteins in its own infection cycle. HDV can exacerbate symptoms and progression of HBV infection (Farci and Niro, 2012).

Prognosis

HBV infections cannot be cured, but a functional cure can be effected in many patients through treatment with pegylated interferon and/or nucleo(t/s)ide analogues to suppress viral replication and eliminate circulating virus and antigens.
Suppressing the virus in patients with an active infection reduces the risk of developing HBV-associated pathologies, including hepatocellular carcinoma (Kuo and Gish, 2012; Liaw, 2013). However, because the viral DNA is still present, since it integrates into the host genome, functionally cured patients experiencing immunosuppression are at risk of virus reactivation (Nebbia et al., 2012).

Oncogenesis

HBV does not have direct cytopathology associated with infection, and oncogenesis is instead attributed to chronic inflammation of the liver - causing fibrosis, cirrhosis, and eventually hepatocellular carcinoma - and the ability of the viral DNA to integrate randomly in the host chromosomes, resulting in loss of cellular regulation. The viral protein HBx manipulates cell cycle progression and host cell transcription patterns (including transcription of miR-122), and truncated mutants have been implicated in tumour production. Certain HBV mutants and HBV genotype C are also associated with higher risk of oncogenesis (Fallot et al., 2012).

Up-regulated by alcohol consumption

Note

Alcohol consumption appears to up-regulate miR-122 expression, which in turn suppresses expression of Cyclin G1 (Hou et al., 2013).
This may be mediated by production of HSP90, and its interaction with the protein GW182, which is involved in the microRNA silencing pathway (Bukong et al., 2013).
In a rat model, miR-122 levels in the liver were significantly increased after chronic alcohol exposure (three weeks) (Dippold et al., 2013). This is believed to have a positive effect on hepatitis C Virus replication (Bukong et al., 2013; Hou et al., 2013).

Non-alcoholic fatty liver disease (NAFLD) and steatohepatitis (NASH)

Note

miR-122 was downregulated in rats fed different diets that induce non-alcoholic fatty liver disease (Alisi et al., 2011). Mice fed with a high fat (NAFLD-inducing) diet, then treated with a miR-122 antagonist, demonstrated lowered serum cholesterol and some lipogenic genes were downregulated (Esau et al., 2006).
Liver biopsies of patients with non-alcoholic steatohepatitis, on the severe end of the NAFLD spectrum, identified significantly lowered levels of miR-122 in these patients, in comparison to healthy control patients; this is suggested to dysregulate lipid metabolism and exacerbate the disease (Cheung et al., 2008).
However, increased serum levels of miR-122 positively correlated with disease severity in NAFLD patients, although this may not be mechanistically associated with the disease (Cermelli et al., 2011).

Hyperlipidaemia and coronary artery disease

Note

Blood plasma levels of miR-122 were elevated in patients with hyperlipidaemia; levels of miR-122 positively correlated with severity of coronary artery disease in patients, and also correlated with increased serum levels of total cholesterol, triglycerides, and low-density lipoprotein cholesterol in both control and diseased patients (Gao et al., 2012).

Cardiac arrest

Note

miR-122 has been identified as a potential biomarker for neurological outcome after cardiac arrest. In a porcine model of cardiac arrest, high levels of plasma miR-122 were detected after induction of cardiac arrest (Andersson et al., 2012). Although miR-122 was not correlated with inflammation or cardiac damage, in a human study, increased serum levels of miR-122 were found in patients with poor neurological outcome (miR-122 is expressed at low levels in neurons) and were associated with elevated mortality (Stammet et al., 2012).

Sepsis

Note

Reduced serum levels of miR-122 were identified in patients with sepsis, as compared to non-septic patients. However, the degree of reduction did not correlate with severity of sepsis (Wang et al., 2012a).

Borna disease virus (BDV)

Note

Borna disease virus is a neurotropic virus that has been identified to contain miR-122 binding sites. Functional assays determined that miR-122 exerts a direct suppressive effect on viral replication and translation; it also appears to indirectly impact viral replication by enhancing interferon signaling (Qian et al., 2010).

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